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Documents Management Branch

Food and Drug Administration

HFA-305

5630 Fisher's Lane, Room 1061

Rockville, MD 20852

23 July 1999

Re: Comments On Docket No. 99D-0674; Guidance for Industry INDs for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products-Chemistry, Manufacturing, and Controls Content and Format

Dear Sir/Madam:

Procter & Gamble Pharmaceuticals wishes to thank the agency for the opportunity to review the above draft guidance. We recognize the fact that a considerable effort has been placed in drafting this document and that this document should be very helpful to industry in providing guiding principles during drug development.

We have reviewed the draft guidance and have the following comments and suggestions (as attached).

If there ~~are~~ any questions or if I can be of further assistance, please feel free to call me at (513) 622-1811.

Sincerely,

Gopi K. Vudathala, Ph.D

99D-0674

C14

Overall, the guidance provides clarity on the CMC requirements for Phase 2 and 3 IND's which should be very helpful to the industry in preparing future IND's and associated amendments.

In the management of INDs as they go from Phase 1 to Phases 2 and 3, the guidance does not establish a clear vision of what is expected. Parts of the guidance focus on "safety updates" while other sections request very detailed information that might better be part of the NDA. Much of the information requested in the Phase 3 section seems to be a preview of the NDA information at the same level of detail that might be expected in that submission. Although the regulations do provide for increasing detail in the later stages of development, the IND does not provide a good format for previewing NDA information and plans. An end of Phase 2 CMC meeting with the division to review the status of development and commercialization plans would address NDA issues more directly and not burden the IND with levels of detail that are not likely to be useful.

The information in lines 80-84 that clarifies when an information amendment is expected and what can be provided in the annual report is very useful and should be retained. However, the guidance seems to imply that there should be a general update at the end of Phases 1 and 2, but does not clearly say that. The underlying principle for the IND should be that it provides adequate information to allow FDA to ensure safety during clinical studies. After the initial IND submission, updates should be provided whenever there are significant changes that could affect safety. Less significant changes should be reported in the annual report. The level of detail should be sufficient to address safety concerns, but not approach NDA levels as the guidance now requests for Phase 3 studies. If the IND is kept up-to-date in this way, there should be no need for major submissions linked to the clinical phases of investigation. Finally, there is no request for an update to the introduction provided for Phase 1. It seems that an update to that would be appropriate.

There ~~are~~ a number of definitions incorporated in the text, The flow might be better if these were collected in a glossary. Similarly there are several sections that provide comment on good development practices. Some people may find these useful, but it does not directly address the format and content of INDs. If FDA thinks these are necessary, they would be better placed in an appendix or a "principles of development section."

Specific comments on the draft guidance with reference to line numbers follow.

Line(s)	Comments
66-75	The reference to data to corroborate the quality and safety criteria established in earlier phases (21 CFR 312.22) needs to be clarified.
81-88	The clarification of what should be an information amendment and what can be an annual report is excellent. The same principle should apply to Phase 2.
86-87	The statement "a change to the synthesis resulting in different impurity profiles" is very broad. If interpreted conservatively, it would require submission of many small changes. More definition should be provided as to what level of changes need to be reported to the agency.
118 - 120	The term "Safety updates" is used in several places in the document but is undefined. Specific examples of what data is necessary should be provided. Further, 'safety updates' could be defined as any information that could cause the agency to revise its assessment of the safety of the drug.
120-121	It is unclear what detailed information is necessary here (3-D structures or configuration?). The structures of the drug are provided in the Phase 1 IND. Does this really pertain to biologics? More clarity on the information required and what constitutes a "complex organic compound" is needed.
130-133	The section regarding the definition of the starting materials, appears to be "pre-work" of part of an NDA issue which is better worked in a direct dialog between the sponsor and FDA. It is suggested that the discussion of starting materials be deleted.
136-139	It should be stated that any updates to information submitted in the phase 1 IND should be provided.
141-142	It is suggested that these lines be deleted since the revised flow diagram requested in the following paragraph (lines 148-153) would include updated information on reagents solvents and auxiliary materials. Further, as stated earlier re: safety updates (lines 118-120), the specific data necessary to be provided on reagents, solvents, and auxiliary materials should be outlined in the following paragraph (starting on line 148).
164 -176	This section contains a high level of detail, but does not actually request any specific information on the reference standard. It is suggested that this be moved to a separate development or principles section.

Line(s)	Comments
173-174	The primary/secondary reference standard approach is not consistent with the approach used by our company for establishment of reference standards. Each standard lot is fully characterized independent from the characterization of a previous standard lot. This includes the use of absolute methods which do not require standard comparison. In some cases there may be a comparison back to a previous lot for a qualitative test e.g., x-ray, but for the most part, the testing is completed independent of previous lot comparison. The approach may vary in other companies and therefore any suitable approaches should be allowed.
180 -187	This section does not pertain to the format and content of the IND but rather is a definition. It is recommended that it be moved to the glossary and/or development section.
189	The phase 1 guidance requests tests and acceptable limits, not specifications. It is recommended that the Phase 2 and 3 guidance continue to use the term 'acceptable limits' since the term 'specifications' implies a more robust requirement, which should not apply during the IND phases as the development of the drug progresses.
192	It is requested in the guidance that any changes in the acceptance criteria are stated. It should be clarified how this is different than the change in specifications requested in line 189.
193-194	Clarification on the data requested is necessary. The statement implies that we need to provide a C of A to the FDA for every lot of drug substance used in clinical production. If this is a correct interpretation, it is unclear why this is necessary. The specifications (or acceptance criteria) are filed to the IND and any drug substance material used in a clinical product will meet the registered acceptance criteria. Internal GMP systems ensure that this is the case. A representative C of A should suffice. Also, what is the intended difference between test results, analytical data, and certificates of analysis? A certificate of analysis by definition, will contain test results and analytical data.
199 - 200	The definition of the container-closure system is suggested to be moved to the glossary.
204	Delete "(or drug product)".since this pertains to the drug substance.
213 - 215	It is suggested that this be moved to a separate development principles section.
217	It should not be necessary to provide a formal stability protocol at this stage since the commercial process may as yet be undefined. The stability data to support the use of clinical product in the study should be sufficient at this phase. The NDA stability protocol would best be discussed at a pre-NDA or end of phase 2 meeting with the agency.

Line(s)	Comments
235-237	It is suggested that this be moved to a separate development principles section.
245-246	It is indicated that "analytical procedures and acceptance criteria should be provided for noncompendial components." However, for both the drug substance (lines 191/192) and drug product (lines 281/282) it states that analytical procedures should be "available on request." This appears to be inconsistent. Why is the methodology for non-compendial components considered to be more critical such that it needs to be provided up front, while drug substance/product methods are to be provided only "on request"? Our experience with non-compendial components (i.e., film coat, dyes) is that they are innocuous with simple methodology. If the intent is to provide a brief method statement (e.g., HPLC, IR, etc.), this should be clarified.
264 - 265	It is suggested that "safety related reprocessing information" be clarified or defined.
267-268	Details of specifics required regarding safety updates on the manufacturing process should be outlined.
276-282	The difference between line 276 which states "Changes to the specification should be reported." and lines 282-3 which state "Any changes in the tentative acceptance criteria should be stated for each test performed." should be clarified.
286-287	Again, "test results, analytical data...and C of A for lots of the drug product used in clinical studies" are requested. As commented above for the drug substance, it's not completely clear what is intended here and clarification is sought. C of A of a lot(s) representative of what is to be used in Phase 2 should be adequate. Also, a summary table of test results is requested but, if a summary table is provided then why is a C of A necessary and vice versa?
304 - 305	The manufacturer may choose to deal with the issue of light stability in a number of ways for a clinical study, e.g. coating, or use of opaque packaging. If so evaluation of the photostability of a clinical product would not be necessary. It is suggested that the reference to stress testing be deleted or modified to "if appropriate."
310 and following	As a general comment, this section appears to be asking for a level of detail normally required in the NDA, at the start of phase 3. The only exception appears to be some flexibility in the manufacturing processes and specifications. It is recommended that the phase 3 section be modified to request summary data more along the lines of phase 2 requirements. Specific comments on this section are provided below.

Line(s)	Comments
340-341	The statement "A list of all firms associated with the manufacturing and controls of the drug substance should be provided, including contract laboratories for quality control and stability testing." implies that manufacturing would not be contracted out. The following statement is proposed: "A list of all firms associated with the manufacturing, controls, and stability evaluation of the drug substance should be provided, including any contract laboratories used to perform any of these functions.
376	Brief description of the analytical procedures are requested. Clarification on what "brief" means should be provided.
387-388	It is stated that analytical procedures and calibration results for the working standard against the primary reference material should be provided. As commented above under phase 2 (line 173-174), this is not consistent with how our company certifies reference standards. Other alternative approaches should be allowed.
400-404	A complete description of the non-USP analytical procedures is requested in the guidance. This level of detail is normally required in the NDA rather than at phase 3. It is suggested that a summary of the analytical procedures and validation be sufficient at this phase.
404	The guideline referenced is in error. It may have been the intent of the agency to refer to the ICH guidelines for analytical methodology and validation.
408-409	The establishment of suitable limits should be based on manufacturing experience and any available safety information. It is suggested that the sentence be rephrased accordingly.
425-431	It is suggested that this section be moved to the development principles section. Specific data that is required in the IND needs to be outlined.
455 - 462	The requested information will mostly be redundant to what is already provided in phase 1 and 2. It is suggested that only updated or new information be requested here.
489 - 490	The statement on planning batch sizes should be in a development principles section.
510	The identification and qualification of degradation products is an ICH requirement and the level of information requested at this phase is considered excessive.
522-523	The data on the container/closure system requested is considered too detailed for submission in the IND. If it's a conventional package, then no information should be necessary to be submitted.

Line(s)	Comments
532-535	The need for a one time stress study should be clarified. Is this meant to be accelerated stability or is this forced degradation studies? Forced degradation studies can be a complex and unrealistic challenge to the drug product. Forced degradation on the drug product is currently not done with the exception of photostability. We rely on the use of related impurities, stability studies and forced degradation of drug substance to challenge the capability of analytical methods. It is suggested that this requirement be deleted in the guidance.
541 -542	Dissolution profiling is considered excessive for the IND. This will be provided for the commercial dosage form in the NDA. In neither filing should it be considered a stability issue. It is suggested that this requirement be deleted in the guidance.
558-559	Does this statement refer to container-closure integrity? If so, it should be clarified.
566-567	It is not considered necessary to include data demonstrating the absence of the active ingredient in the IND for phase 2 and 3. The methods and acceptance criteria for the placebo, which would include a test for absence of the active, should be adequate to meet the needs of the reviewer.
581-583	While a disclaimer statement is provided indicating that the ICH guidelines are not intended for IND applications, the body of the guidance is not consistent with this message. Although specific ICH guidelines are not referenced, the phase 3 part of the guidance reflects much of the ICH requirements. It is recommended that the level of detail required in the phase 2 and 3 guidance be reduced to specific information that is safety related.

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